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The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference*

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Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; CDC, Centres for Disease Control; ECDC, European Centre for Disease Prevention and Control; ELPA, European Liver Patients Association; EMA, European Medicines Authority; EMCDDA, European Monitoring Centre for Drugs and Drug Abuse; EU, European Union; GPs, General Practitioners; HBc, Hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IDUs, injecting drug users; MSMs, men who have sex with men; NS5a, nonstructural protein 5a; SMR, standardized mortality rate; STD, sexually transmitted disease; SVR, sustained virological response; VHPB, Viral Hepatitis Prevention Board.

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*This paper presents the summary findings and conclusions from the Hepatitis B and C Summit Conference, held in Brussels in October 2010.

SUMMARY. Worldwide, the hepatitis B virus (HBV) and the hepatitis C virus (HCV) cause, respectively, 600 000 and 350 000 deaths each year. Viral hepatitis is the leading cause of cirrhosis and liver cancer, which in turn ranks as the third cause of cancer death worldwide. Within the WHO European region, approximately 14 million people are chronically infected with HBV, and nine million people are chronically infected with HCV. Lack of reliable epidemiological data on HBV and HCV is one of the biggest hurdles to advancing policy. Risk groups such as migrants and injecting drug users (IDU) tend to be under-represented in existing prevalence studies; thus, targeted surveillance is urgently needed to correctly estimate the burden of HBV and HCV. The most effective means of prevention against HBV is vaccination, and most European Union (EU) countries have universal vaccination programmes. For both HBV and HCV, screening of individuals who present a high risk of contracting the virus is critical given the asymptomatic, and

thereby silent, nature of disease. Screening of migrants and IDUs has been shown to be effective and potentially cost-effective. There have been significant advances in the treatment of HCV and HBV in recent years, but health care professionals remain poorly aware of treatment options. Greater professional training is needed on the management of hepatitis including the treatment of liver cancer to encourage adherence to guidelines and offer patients the best possible outcomes. Viral hepatitis knows no borders. EU Member States, guided by the EU, need to work in a concerted manner to implement lasting, effective policies and programmes and make tackling viral hepatitis a public health priority.

Keywords: Europe, hepatitis B, hepatitis C, liver cancer, policy.

INTRODUCTION

Hepatitis B (HBV) and C (HCV) virus infections constitute a major global public health threat. About 2 billion people have been infected with HBV, of whom 350 000 are chronically infected. Between 130 and 170 million people are chronically infected with HCV worldwide. Approximately 600 000 and 350 000 deaths each year occur as a result of HBV and HCV infections, respectively [1]. Chronic hepatitis B and C are leading causes of cirrhosis and hepatocellular carcinoma (HCC), which ranks as the third cause of cancer deaths worldwide. Globally, 2.7% of all deaths are because of liver cancer and cirrhosis resulting from HBV and HCV, and this percentage is increasing over time. Hepatitis B is thought to be 50–100 times and hepatitis C up to 10 times more infectious than human immunodeficiency virus (HIV) [2,3].

In Europe, the threat posed by chronic viral hepatitis is becoming more apparent. Within the World Health Organisation (WHO) European region, about 14 million people are chronically infected with hepatitis B, and nine million people are chronically infected with hepatitis C, in comparison with 1.5 million infected by HIV. Thirty-six thousand people die each year because of HBV-related causes and 86 000 because of HCV (N. Emiroglou, WHO data presented at Hepatitis B and C Summit Conference, October 2010).

Despite these staggering figures, there is little understanding at the public or policy level of the health implications of hepatitis B and C in the European Union (EU) or elsewhere (see Panel 1). Surveys conducted by the European Liver Patients Association (ELPA) suggest that up to 90% of infected people in the EU are unaware of their condition. Among diagnosed individuals, 20% said they had never heard of viral hepatitis at the time of their diagnosis, and 27% did not know that they were at high risk of transmitting the infection [4]. Similar figures were reported by the Institute of Medicine [5] report in the United States, which stated that 65% of those infected with HBV and 75% of those infected with HCV admitted that they were unaware of their condition. Lack of awareness on the part of health care and social service providers might partly explain why both HBV and HCV are generally under-diagnosed and under-treated. At the policy level, viral hepatitis is often not recognized as a serious but treatable public health problem, and therefore, the resources allocated towards its prevention and man-

PANEL 1: SUMMARY FINDINGS OF THE INSTITUTE OF MEDICINE REPORT

In 2010, the US Centres for Disease Control and Prevention (CDC), along with the Department of Health and Human Services and other federal bodies, asked the Institute of Medicine to 'identify missed opportunities related to the prevention and control of HBV and HCV infections'. The ensuing report has relevance far beyond the US context. Summary findings and recommendations are summarized below:

Factors that impede current efforts to prevent and control hepatitis B and hepatitis C are as follows:

- There is a lack of knowledge and awareness about chronic viral hepatitis on the part of health care and social service providers
- There is a lack of knowledge and awareness about chronic viral hepatitis among at-risk populations, members of the public and policymakers
- There is insufficient understanding about the extent and seriousness of this public health problem, so inadequate public resources are being allocated to prevention, control and surveillance programmes.

The consequences of this situation are as follows:

- Inadequate disease surveillance systems underreport acute and chronic infections, so the full extent of the problem is unknown.
- At-risk people do not know that they are at risk or how to prevent becoming infected.
- At-risk people may not have access to preventive services.
- Chronically infected people do not know that they are infected.
- Many health care providers do not screen people for risk factors or do not know how to manage infected people.
- Infected people often have inadequate access to testing, social support and medical management services.
- There is suboptimal coverage of HBV vaccination.

Adapted from [5].

agement are largely insufficient. The EU still lacks a unified comprehensive strategy to tackle viral hepatitis, and many EU Member States have done relatively little to establish robust viral hepatitis policies and programmes.

The hepatitis B and C summit conference

It is against this background that the hepatitis B and hepatitis C Conference was created. The Conference involved a wide range of stakeholders in a vigorous partnership whose goal is to curtail the growing and evolving impact of hepatitis B and C in Europe through effective polices and targeted actions.

The Conference held its first summit on 14–15 October 2010 bringing together expert clinicians, public health specialists, patient groups, EU and national policymakers. This paper presents the main findings and conclusions drawn from the conference and includes the Call to Action for the EU and Member States on hepatitis B and C. Conference presentations and background documents may be found on the Conference website, http://www.hepsummit2010.org.

EPIDEMIOLOGY

Surveillance

Mandatory surveillance of both hepatitis B and C is common across all of Europe, and a common data set is collected in most Member States. However, there is great heterogeneity in surveillance protocols in terms of case definitions used. Most surveillance focusses on acute, usually symptomatic, cases or, in the case of HBV, does not distinguish between acute and chronic cases. There is little possibility for linking existing registries because of the lack of an established network, such as exists in the case of HIV/acquired immunodeficiency syndrome (AIDS). Available data on hepatitis C in particular may be more a reflection of existing screening practices and laboratory test data rather than actual epidemiological surveillance. In light of these deficits, the European Centre for Disease Prevention and Control (ECDC) included hepatitis B and C in its enhanced surveillance programme as of 2010, in the hope of greatly improving the quality and reliability of epidemiological data on hepatitis B and C in Europe [6].

Prevalence of hepatitis B and C

The prevalence of chronic HBV infection in the general population ranges from 0.2% in Ireland and the Netherlands to over 7% in some parts of Turkey. The prevalence of HCV also varies from 0.4% in Sweden, Germany and the Netherlands to over 2–3% in some Mediterranean countries. High-risk, vulnerable groups such as IDUs, migrants, homeless persons and prisoners tend to be under-represented in general population studies, so that prevalence figures for these populations are likely to be considerably underestimated, especially in low-prevalence countries [7].

Complications

The natural history of chronic hepatitis B is complex and highly variable. The incidence of cirrhosis is 0.1% per year in inactive carriers of hepatitis B surface antigen (HBsAg) and 2–10% per year in individuals with chronic hepatitis B. The 5-year cumulative risk of developing HCC in cirrhotic patients varies by region: it is 17% in East Asia and 10% in Europe and USA. The 5-year liver-related death rate in cirrhotics is 15% [8]. The risk of complications depends on factors, such as gender, age, severity of liver disease, co-infections [such as hepatitis D virus (HDV), HCV and HIV], HBV replication status and external factors such as alcohol intake, smoking and environmental carcinogens (such as aflatoxins) [9]. Serum HBV-DNA level is a direct measure of HBV replication and a major predictor of cirrhosis and HCC. Other independent predictors of cirrhosis are male sex, older age, hepatitis B e antigen positivity and elevated alanine aminotransferase (ALT) [10,11].

The natural history of chronic hepatitis C is also highly variable (Table 1). The progression of chronic hepatitis C is related to nonmodifiable factors, such as age at infection, sex, race, and host genetics, and potentially modifiable factors such as ALT levels, alcohol consumption, uncontrolled co-infections (HIV, HBV, schistosomiasis), cigarette smoking, cannabis use, iron overload, liver steatosis and insulin resistance [12,13].

Both hepatitis B and C are associated with excess mortality. In a recent study that examined all diagnoses of HCV made in Scotland between 1991 and 2006, HCV-infected individuals had a higher all-cause and a higher liver-related mortality rate compared to the general population, even after allowing for deprivation [standardized mortality rate (SMR) for overall mortality 3.41 (95% CI 3.3–3.5), for liver-related diagnoses SMR 41.3, 95% CI 39.6–43.0] [14].

Primary liver cancer (HCC)

The heavy toll of HCC in Europe has only become clear over the past 10–15 years. In Europe, 60–70% of HCC cases are caused by HCV, 10–15% by HBV, 20% by alcohol and 10% by other causes [15–17]. The relative importance of different risk factors varies by region (Table 2). Cirrhosis remains the greatest risk factor for HCC: the risk of HCC is 15–20% in cirrhotic patients, and the number of cirrhosis cases is increasing in Europe [9,18,19]. The incidence and risk of death attributed to liver cancer appear to be highest in Southern Europe for both men and women. However, differences between countries may reflect different screening and testing practices rather than actual epidemiology.

Table 1 Natural history of hepatitis C from retrospective, prospective and retrospective–prospective cohort studies (modified from [12])

Retrospective Studies	
Intervals from exposure	9–29 years
Cirrhosis	17–55% (mean 42%)
HCC	1–23%
Liver deaths	4–15%
Prospective studies	
Intervals from exposure	8–16 years
Cirrhosis	7–16% (mean 11%)
HCC	0.7–1.3%
Liver deaths	1.3–3.7%
Retrospective–Prospective cohort studies	
Children and young men or women	
Exposure interval	9–45 years
Cirrhosis	0.3–5.9% (mean 2.1%)
HCC	0
Liver deaths	0–2.1%
Middle-aged people with post-transfusion hepatitis	
Exposure interval	23 years
Cirrhosis	15%
HCC	1.9%
Liver deaths	2.8%

HCC, hepatocellular carcinoma.

Table 2 Risk factors for hepatocellular carcinoma (HCC) worldwide, by geographic area, 2000. Adapted from [16]

	Risk Factor (%)			
	Hepatitic C virus	Hepatitis B virus	Alcohol	Other
Europe	60–70	10–15	20	10
North America	50–60	20	20	10
Asia* and Africa	20	70	10	<10†

*Except Japan, where HCV accounts for 70%, HBV for 10–20%, alcohol for 10% and others <10% of cases.
†Aflatoxin is main co-factor enhancing oncogenetic risk of patients with HBV infection.

VACCINATION AGAINST HEPATITIS B

Universal vaccination against hepatitis B has been advocated by the WHO since 1991, and 177 countries have currently implemented universal vaccination programmes worldwide with an outstanding record of safety and efficacy. Vaccination has been clearly shown to reduce the incidence, carrier rates and mortality related to hepatitis B. Taiwan is perhaps the best example of a previously highly endemic area, which has shown a substantial decrease in the burden of hepatitis B and HBV-related diseases following the introduction of mass vaccination of newborns in 1984. The annual average incidence of HCC among children declined significantly after the implementation of vaccination in Taiwan, demonstrating clearly that hepatitis B vaccine is the first vaccine that can prevent a major human cancer [20]. Likewise, in other previously endemic areas (for example, the Gambia, Malaysia and Alaska), vaccination has proven to be very successful.

Within the European region, most countries offer universal vaccination. However, the UK and Scandinavian countries still do not advocate universal vaccination and have opted on economic grounds for targeted vaccination focussed on well-defined risk groups. Surveillance data from Italy, where universal vaccination started in 1991 in infants as well as in adolescents, have shown a remarkable overall decline in incidence of acute hepatitis B after the implementation of vaccination [21] (Fig. 1). Moreover, a generation of children and young adults (at present aged <32) is emerging with practically no markers for HBV infection. In addition, because of the virological association between HBV and HDV, an added benefit of vaccination is that the decline in incidence of hepatitis B has caused a parallel decline in hepatitis D.

Subclinical infections characterized by the appearance of anti-HBc antibody or transient elevations of ALT have been occasionally observed in successfully vaccinated people. Infections caused by HBV S-gene mutants, including the prototype glycine to arginine substitution (G145R), have been observed in several countries, particularly Taiwan. Despite the initial concern that these mutants could evade the vaccine-induced immune response and infect vaccinated individuals, at present, they are not known to pose a public health threat [21]. A number of case reports from France in 1998 and thereafter raised concern that hepatitis B vaccination may lead to new cases or relapses of neurological

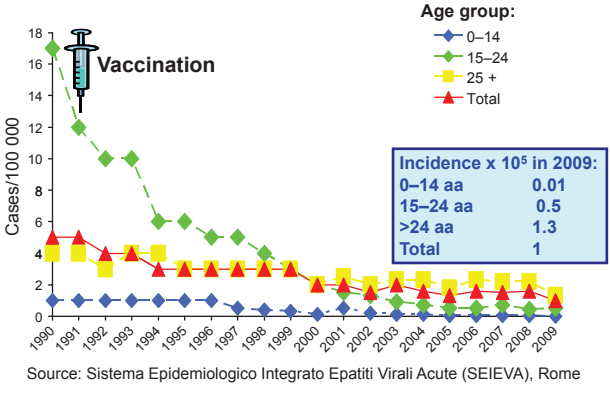

Fig. 1 Morbidity rate ($\times 10^5$ inhabitants) of hepatitis B in Italy, according to age (1990–2009).

diseases; however, no clear causal link has been established [22–24].

Evidence indicates that vaccine-induced hepatitis B surface antibodies (anti-HBs) are long lasting and may persist for over 15 years. Vaccinees who have lost protective (<10 mIU/mL) anti-HBs antibody usually show a rapid anamnestic response when boosted [25]. This means that immunological memory for HBsAg can outlast antibody detection, providing long-term protection against HBV infection and the development of the carrier state [26]. Hence, for immunocompetent individuals, booster doses of vaccine do not seem necessary to ensure long-term protection [27–29].

Globally, remarkable progress in the introduction and implementation of vaccination against hepatitis B has been achieved in recent years, but much remains to be done to meet the WHO goal of controlling hepatitis B in the community at large. At present, most countries not yet covered by vaccination are those of low economic status and high endemicity. Thus, efforts are urgently required to override the economic barriers that hamper both the standard of living and the implementation of universal vaccination policies in such countries. In addition, extensive migration and travel to and from highly endemic countries may increase the risk of exposure to the virus, thereby necessitating a global strategy for the control of HBV infection. Based on the positive impact of hepatitis B vaccination, support for further development of hepatitis C vaccine research has been expressed.

HBV AND HCV SCREENING

Close to three-quarters of people infected with HCV or HBV are unaware of their condition; thus, screening of high-risk populations is paramount if one is to identify infected individuals and offer them appropriate management [4,5]. Targets for screening vary from one programme to another and may include blood, tissue and organ donors, pregnant women, health care workers, IDUs, men who have sex with men, sex workers, subjects with promiscuous sexual behaviour and migrants from high-prevalence areas. Ideally, all subjects with symptoms and signs of liver disease, including those with elevated serum aminotransferases, as well as household and sexual contacts of HBV- or HCV-positive subjects should be screened for HBV and HCV, as appropriate. Moreover, all individuals with positive HBsAg should be screened for hepatitis delta virus, given that chronic hepatitis delta is the most aggressive form of viral hepatitis.

In its most recent report on viral hepatitis, the ECDC conducted a review of screening practices and studies in Europe [7]. The report reveals striking heterogeneity in screening practices across the EU. For example, a number of countries still do not offer hepatitis screening to pregnant women, thereby forfeiting the critical opportunity to prevent mother-to-child transmission. Screening among blood donors is, by contrast, systematically undertaken across the EU. There is a general lack of information on the cost-effectiveness of screening high-risk groups for viral hepatitis. Only two studies were identified, and both suggested that screening of migrant groups for HBV and HCV was both clinically effective and cost-effective [30,31]. The evidence supporting screening for IDUs is somewhat more favourable, particularly for HCV. However, implementation of screening policies and uptake of screening among IDUs is reported to be very low and fragmented as many drug treatment centres do not offer screening on a routine basis [7]. The limited evidence for cost-effectiveness does not imply that screening is not likely to be cost-effective but that for most high-risk groups where screening might be highly cost-effective, the number of studies is limited [32].

Within the EU, screening programmes are very limited [33], and only France and Scotland have instituted a government-led programme to improve screening of high-risk groups in a sustainable and comprehensive manner. The Scottish programme focusses solely on HCV. The Netherlands has conducted a number of pilot projects offering screening against HBV to Chinese communities. Targeted screening campaigns have also been very successful in other countries, such as the Silesia region in Poland and the Blackpool in England, where mortality rates from chronic liver disease are very high. Some of the main lessons learned from some of these screening programmes are presented in Panel 2.

The Institute of Medicine Report on Hepatitis and Liver Cancer in the USA has recently formulated five core functions for comprehensive hepatitis services: (i) community outreach, (ii) prevention, (iii) identification of infected persons, (iv) social and peer support and (v) medical support. Identification of infected persons is a two-step process: (i) risk factor screening and (ii) serological testing for HBV and HCV [5]. A summary of updated recommendations on screening of high-risk populations for hepatitis B and C from the US Centres for Disease Control (CDC) is shown in Table 3.

TREATMENT

There have been considerable advances in the antiviral treatment of hepatitis B and C over the past decade, such that today viral replication can be effectively suppressed in 95% of cases of chronic hepatitis B and 60% of chronic hepatitis C cases can be cured [34–37]. There is also growing evidence suggesting that treatment options for hepatitis B and C are cost-effective and form part of the control of the disease [38].

Hepatitis B

Hepatitis B has often been termed ‘a silent killer’ as patients often remain asymptomatic – and thereby undiagnosed – for

PANEL 2: CONSIDERATIONS FOR THE IMPLEMENTATION OF SUCCESSFUL SCREENING PROGRAMMES FOR HBV AND HCV

- Develop clear public awareness campaigns targeted at the general public and at risk groups.
- Need a clear clinical strategy to deal with HBV- and HCV-infected persons.
- Revise clinical guidelines to endorse HBV and HCV screening in specified risk groups and reinforce dissemination of best practices for case finding.
- Integrate screening into existing public health and care practices whenever possible.
- Conduct HBV & HCV screening in HIV/STD clinics, prisons, drug user services as well as in primary care clinics.
- Simplify screening criteria, e.g. adopt age-based criteria for HCV, birth place for HBV with the aim of providing clear guidance to GPs and those screening patients.
- Educate providers about the needs for screening and about the management pathways for HBV- and HCV-infected individuals.
- Always carry out screening in an evidence-based way that defines when and how often screening should be offered and respects the human rights of those screened.
- Always accompany screening with appropriate counselling of the individual and his or her family.
- In the case of marginalized or stigmatized groups such as migrants or IDUs, one must ensure that individuals are not stigmatized because of their group membership or their viral hepatitis status.

Table 3 Updated summary of Centres for Disease Control recommendations for high-risk populations for hepatitis B and hepatitis C (adapted from [5])

Hepatitis B
Persons born in geographic regions that have hepatitis B surface antigen prevalence of at least 2%
Infants born to infected mothers
Household contacts of persons who have chronic HBV infection
Sex partners of infected persons
Injection-drug users
Sexually active persons who are not in long-term, mutually monogamous relationships (for example, more than one sex partner during previous 6 months)
Men who have sex with men
Health care and public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids
Residents and staff of facilities for developmentally disabled persons
Persons who have chronic liver disease
Haemodialysis patients
Travellers to countries that have intermediate or high prevalence of HBV infection
Hepatitis C
Persons who have ever injected illegal drugs, including those who injected only once many years ago
Recipients of clotting factor concentrates made before 1987
Recipients of blood transfusions or solid-organ transplants before July 1992
Patients who have ever received long-term haemodialysis treatment
Persons who have known exposures to HCV, such as
Health care workers after needlesticks involving HCV-positive blood
Recipients of blood or organs from donors who later tested HCV positive
All persons who have HIV infection
Patients who have signs or symptoms of liver disease (for example, abnormal liver enzyme tests)
Children born to HCV-positive mothers (to avoid detecting maternal antibody, these children should not be tested before the age of 18 months)

several years and even decades. Even once diagnosis is made, active treatment rates remain very low, despite cumulative evidence that early treatment and viral suppression greatly reduce the risk of progression to cirrhosis, liver cancer and eventual death [8,36].

Treatment is usually focussed on the immune-active phases of disease when rates of progressive fibrosis are increased. The goals of treatment for hepatitis B are to prevent cirrhosis, hepatic decompensation and HCC and thereby to improve mortality rates and quality of life by preventing progression of the disease [39]. The two possible treatment approaches include either stimulating the immune system (through pegylated interferon) or suppressing viral load through nucleo(t)side analogues. An illustration of treatment options is presented in Fig. 2. Most recent research efforts have focussed on nucleo(t)side analogues. Given that patients may be receiving treatment for an extended period of time, potent and safe agents with a low rate of resistance are favoured. The most recently available agents for hepatitis B (tenofovir and entecavir) show promising resistance profiles; however, patient adherence remains challenging, especially during asymptomatic phases of the disease. Combination with pegylated interferon should be further evaluated to assess the possibility of finite or reduced duration treatment regimens.

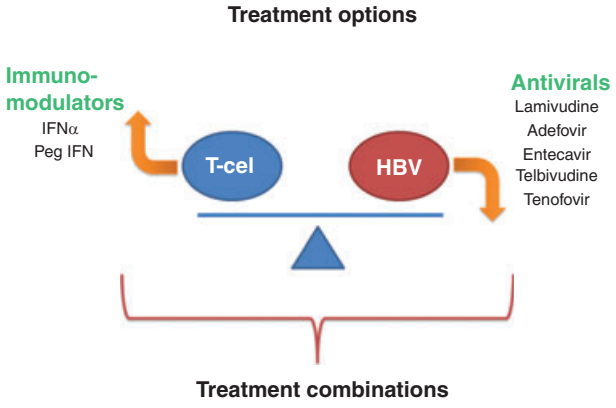

Fig. 2 Treatment options for hepatitis B.

Hepatitis C

With appropriate treatment, clearance of circulating HCV RNA or a sustained virological response (SVR) that is considered tantamount to a cure of chronic hepatitis C can be achieved in up to 60% of cases, effectively resulting in a reversal of the natural history of the disease [40,41]. Currently, combination therapy using pegylated interferon and ribavirin is the most widely used treatment option. Side effects include neutropenia, anaemia and depressive or other mood changes. The search for improved cure rates is being actively pursued, and tailored treatment algorithms based on the kinetics of response to treatment and genetic variations of the host are being developed [40,41]. Several new therapeutic options, using direct antiviral agents including, for example, first-generation protease inhibitors (boceprevir, telaprevir) in combination with pegylated interferon and ribavirin, have completed phase 3 clinical trials for patients infected with HCV genotype 1 and have recently been approved for use in the United States and are awaiting imminent approval in Europe. These new regimens improve the efficacy of treatment in genotype 1 HCV. A large number of second-generation protease inhibitors, polymerase inhibitors, nonstructural protein 5a inhibitors as well as host-acting antiviral agents are currently in phase 2 and 3 assessment.

Treatment of advanced disease

The treatment of advanced liver disease, including liver cancer, has been transformed in the past 20 years. Several studies have provided histological evidence that cirrhosis can in part be reversed in patients infected with HBV and HCV [36,42]. Twenty-five years ago, liver cancer was thought to be incurable. Yet today, multiple treatment options exist, such as treatment with surgical resection, liver transplantation, percutaneous ablation, transarterial chemoembolization and sorafenib, which have demonstrated improved survival in patients with liver cancer [43,44]. Physicians outside of specialist centres need to be better informed about treatment options for patients with liver cancer and made aware of existing guidelines for the surveillance and management of liver cancer to ensure that they guide their patients towards appropriate care [44,45].

VULNERABLE POPULATIONS

Migrants

Despite the fact that a large proportion of migrants into the EU come from countries of high endemicity for HBV and HCV, the topic of viral hepatitis and migration has received little attention thus far [46].

Prevalence rates of HBV and HCV obtained from migrants are much higher than those obtained from general population surveys – in which migrants tend to be under-represented. For example, a German study estimated that there were approximately half a million HBV carriers in Germany in 2005, of whom individuals from a migrant background accounted for 43%, when they only make up 13% of the general population [47].

Migrants may face several barriers to prevention and care that need to be acknowledged in all policies and programmes for hepatitis B and C. Poverty, distance and poor transportation, limited access to care, literacy rates, levels of parental education (in the case of children) and cultural, linguistic and religious differences or administrative rules may all act as barriers for migrants to access vaccination, screening and other hepatitis services [48,49].

Illegal migrants present particular challenges as they are not acknowledged by (or known to) public health authorities and they are largely inaccessible to health initiatives. As was suggested in a special report commissioned for the Conference on the topic of migration and viral hepatitis, 'the conditions of life, marginalization from health care systems and reluctance/fear of being identified by judicial authorities make the task of reaching illegal migrants with screening, early diagnosis and treatment difficult' [46].

The diversity of needs among migrant communities must be taken into account in all policies and programmes to ensure that actions are culturally sensitive and appropriate. We need to gain a better understanding of the prevalence, disease burden and barriers to care faced by migrant communities across Europe to ensure that the burden of hepatitis B and C is reduced within this vulnerable population [46].

Injecting drug users

Injecting drug users constitute a large proportion (40%) of notified acute cases of hepatitis C, suggesting that currently they are a very important risk group for new infections [50]. In the EU, HCV is far more prevalent than HBV or HIV among IDUs and often reaches extremely high levels. Data from seroprevalence studies routinely collected by the European Monitoring Centre for Drugs and Drug Abuse

(EMCDDA) suggest that the prevalence of serological markers for HBV and HCV is much higher in IDUs than in the general population. However, general notification data on hepatitis B and C are very poor, with levels of under-diagnosis and under-reporting that may reach up to 50–98% [51,52]. Therefore, despite having their own limitations, seroprevalence studies specifically targeted at IDUs and other risk groups are important.

Guidelines for testing IDUs for HIV, viral hepatitis and other infections have recently been published by the EMCDDA [52]. Evidence suggests that treatment of active IDUs with antiviral therapy may be one of the best ways to contain the burden of HCV, contrary to existing guidelines that often discourage treating active injectors. A recent modelling study suggests that, based on realistic treatment capacity, treating 40 per 1000 IDUs annually could result in a 70% decrease in HCV prevalence over a 10-year period [53]. The underlying principle of this 'treatment for prevention' approach, also advocated by the HIV/AIDS research community, is that the overall viral load in the population can be reduced through effective treatment of those infected, thereby halting the cycle of transmission [54]. In the case of hepatitis C, sustained viral responses (SVR) in this population pool would result in reduced transmission rates. Currently, <1% of the population of IDUs in the UK is thought to receive active treatment. Data are not available from other countries. The main reason for such low treatment rates is ongoing concern over the safety of interferon in active drug users, potential non-compliance with treatment and risk of re-infection because of ongoing drug use and co-existing psychiatric disorders. A number of studies, however, have found that these problems can be addressed [55,56].

THE STATE OF POLICY

Important strides have been made to raise the profile of hepatitis on the policy agenda in recent years. In May 2010, the World Health Assembly adopted the 63rd World Health Assembly Resolution on Viral Hepatitis. The WHO is adopting a regional strategy for viral hepatitis for the entire European region focussing on three pillars:

- immunization of newborns and high-risk groups against hepatitis B,
- integration of hepatitis prevention and care into national public health programmes and interventions, and
- safe health care services to prevent blood-borne infections (N. Emiroglou, conference presentation).

Hepatitis is also gaining visibility at the EU level. The ECDC included hepatitis B and C in its enhanced surveillance programme in 2011, which promises to greatly improve the evidence base that can underpin the development of targeted programmes and actions. The EMCDDA is annually collecting and reporting data on HCV and HBV seroprevalence in IDUs. The European Commission may also play an important role in guiding hepatitis policy, through its public health and research programmes. The Directorate General for Health and Consumers (DG-Sanco) has funded several projects targeting hepatitis, a full list of which can be found on http://ec.europea.eu/eahc/index.html. DG Research unfortunately has provided very limited support to hepatitis research through its Framework Programme so far. It has engaged in a vaccine effort, HEPCIVAC, which is focussed on finding new preventative and therapeutic HCV vaccines, as well as developing HCV disease predictive biomarkers. In HBV, the focus has been only on HIV–HBV co-infection. And finally, the European Medicines Authority (EMA) has drafted guidance to drug developers on the clinical evaluation of antiviral agents against HBV and HCV [57,58].

Yet, despite these efforts, much work remains to be carried out. An EU Council Resolution on hepatitis B and C is urgently needed. The EU is still characterized by a lack of standardized policies and practices. For example, antenatal screening against hepatitis B and C should be offered to all pregnant women to help prevent mother-to-child transmission of the virus. Whilst it may be argued that the diverse epidemiology of hepatitis B and C warrants policies and programmes tailored to each national epidemiological situation, it should be emphasized that, from an EU public health perspective, 'managing diversity should not mean tolerating unjustified inequalities' (see address by Dr Marc Sprenger, Annex I).

The EU may play a leadership role in public health. However, plans to tackle HBV and HCV must be developed and implemented at the national level. Countries seeking to develop programmes targeting hepatitis B and C may draw lessons from successful initiatives from within and outside the EU which have achieved encouraging results. Some examples of national programmes presented at the Conference are presented in Panels 3 & 4. Finally, it is at the national level that the resources to implement policies and programmes targeting hepatitis B and C are deployed. A recent report published by the Institute of Medicine [5] in the United States pointed to huge gaps in policy and resources devoted to tackling hepatitis B and C and concluded that, despite its significant toll in terms of public health, neither HBV nor HCV receives adequate funding compared to other communicable diseases such as HIV/AIDS. Similar conclusions may be drawn for Europe and point to the urgent need to appropriately allocate funds and resources targeted towards the control and management of viral hepatitis. Nowadays, in most European countries, many more people are dying from the complications of viral hepatitis than from AIDS. Comparative figures for viral hepatitis and HIV regarding awareness and funding from the United States, presented during the conference, are shown in Table 4.

It is against this background that the Conference Summit launched its Call to Action to all policymakers and stakeholders concerned with hepatitis B and C in the EU (Annex II). The EU has a clear mandate in communicable diseases. A Council Recommendation on viral hepatitis will help guide

PANEL 3: KEY FACTORS NECESSARY FOR THE SUCCESSFUL IMPLEMENTATION OF PREVENTION AND MANAGEMENT PROGRAMMES TARGETING HBV AND/OR HCV

- Reliable local epidemiological data to communicate with policymakers
- Clinical leadership from specialist centres as well as from public health, social services and other relevant professional groups
- Motivation of all those involved in programme using quantifiable goals (e.g. 75% of patients with HepC will be aware of their infection by a given year)
- Inclusion of concrete goals to extend treatment in line with existing – and desired – treatment capacity
- Recognition of the need for and potential of therapeutic developments to confer true patient benefits
- Strong, continuous patient advocacy
- Close and ongoing dialogue between patients, clinical leads, public health specialists and policymakers
- Awareness campaigns to increase testing through GPs and other primary care providers
- Systematic referral system for individuals screening positive to secondary care
- Targeted awareness campaigns (e.g. aimed at different immigrant communities)
- Strengthening of network between hospitals, GPs and physicians in special settings (e.g. prisons or sexual health clinics)
- Shared patient management between specialists and GPs to lessen the burden on hospitals.

PANEL 4: THE SCOTTISH AND FRENCH NATIONAL PLANS FOR HEPATITIS

French National Plan for Hepatitis B and C [59]

Achievements:

- Increase in proportion of patients aware of HCV positivity from 24% to 56% (1994–2004) [59]
- Highest treatment rate for HepC in Europe (16% in 2005) [60]
- Demonstrated impact on morbidity and mortality
- Surveillance system implemented as part of National Public Health Plan

Lessons learned:

- Migrants can be reached with outreach campaigns
- Ensure referral to secondary care
- HCV campaigns can increase testing through GPs
- Ensure referral to secondary care
- Motivation of quantifiable goals, e.g. 65% of patients with HepB aware of their infection (HepC: 75%)
- Need to strengthen network between hospitals, GPs and physicians in special settings

Scottish National Hepatitis C Plan

Achievements:

- Managed Care Networks for HepC
- National procurement of antivirals at reduced prices
- Increase in numbers diagnosed, doubling of numbers treated
- Fivefold increase in number of prisoners treated
- New approaches for gauging incidence in IDUs

Lessons learned: four elements needed to secure plan:

- Epidemiological data
- Clinical leadership
- Therapeutic developments
- Patient advocacy

national action. The message to be communicated to EU institutions is that current figures underestimate the true toll of hepatitis B and C and that urgent actions need to be taken at all levels. In particular, more prominence for hepatitis B and C should be sought within public health and research programmes in the next wave of European Commission funding.

CONCLUSIONS

The main conclusions from the Conference can thus be summarized as follows:

Enhanced surveillance of hepatitis B and C is urgently needed

One of the biggest gaps in the advancement of policy on viral hepatitis is the lack of reliable data on the epidemiology of both hepatitis B and C across Europe. There is an urgent need for extensive surveillance networks, for a common protocol for prevalence studies and for improved and more representative epidemiological data overall on both hepatitis B and C.

Vaccination remains the most effective preventive approach against HBV

Within the European region, most countries offer universal vaccination, yet within the EU, seven countries still do not have universal vaccination and have opted instead for tar-

Table 4 Allocation of research funds towards HCV, HBV and HIV in the United States

	HIV	HCV	HBV
Number of people infected (million)	1.05–1.16	2.7–3.9	0.8–1.4
Proportion of those unaware of their condition (%)	21	75	65
National Institutes of Health research funds (US million dollars, 2011 figures)	3.184	102	54

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geted vaccination of at-risk population. The justification for the decision not to offer universal vaccination can be challenged. The coverage of HBV vaccination is low compared to other childhood vaccines and needs to be improved. So, in addition, universal vaccination should be complemented with targeted vaccination of at-risk groups.

More resources must be devoted to screening programmes for risk groups

Vulnerable and risk groups, particularly migrants and IDUs, are under-represented in general population prevalence studies, and active targeted surveillance of these populations is needed to correct existing prevalence estimates. Screening of individuals who are at high risk of having or contracting HBV or HCV is also critical to offer early treatment and prevent carriers from infecting others. Data from the ECDC and other studies suggest that screening of certain risk groups is effective and potentially cost-effective. Screening programmes must always be accompanied by counselling, integrated into existing public health and care practices and connected to treatment programmes to be effective.

Early diagnosis and treatment are essential for both hepatitis B and C

The message that, with treatment, 95% of chronic HBV cases can be effectively treated by current antiviral agents, thereby improving survival, and that 60% of chronic HCV cases can be cured, reversing the natural history, must be delivered clearly to all treating physicians, as well as policymakers and patients themselves. Extending treatment to a greater number of patients not only improves the outcomes but also reduces mortality for those treated, and it has demonstrable public health impact as it reduces infectivity and therefore transmission of HBV and HCV.

The importance of HCC in Europe should be recognized

Liver cancer is the third most important cancer in terms of mortality and the sixth in incidence worldwide. In Europe, data from several countries suggest that mortality from liver cancer is rising. Greater efforts are needed to make the medical community aware of the natural history of liver cancer and its links to HCV and HBV, to improve adherence to treatment guidelines and to convey the importance of screening in HBV and HCV patients to diagnose HCC earlier to improve survival and offer patients the best possible outcomes. Mortality statistics should also include infection status by HBV or HCV.

Successful national and local initiatives provide best practice examples from which important lessons may be learned

It is important to acknowledge that a number of national and local programmes have achieved significant results in curtailing the toll posed by HBV and HCV (see http://www.hepsummit2010.org). Some key lessons derived from these initiatives are that evidence-based and reliable epidemiological data are essential to drive policy, that targeted actions in migrants are effective, that treatment of active IDUs has been shown to be effective and that quantifiable goal, provide important motivation for success.

Patient advocacy groups play a critical role in advancing policy and patient care

Despite chronic shortages of funds and low resources, patient groups provide strong leadership in raising awareness of hepatitis B and C in Europe. They also fill a critical gap by raising awareness and in some cases offering counselling and psychological support to patients that is usually missing from traditional medical centres. The biggest hurdle faced by patient groups, apart from funding shortages, is the low level of interest or awareness among general practitioners, which in turn limits the opportunities for increasing screening and diagnosis of individuals infected with either HBV or HCV. More initiatives that help engage general practitioners in improving the prevention, screening and care of hepatitis B and C are urgently needed.

Europe must recognize the importance of viral hepatitis and make resources available to deliver policies

To quote MEP Alojz Peterle in his address to the Summit Conference, 'the need for additional data must not be an excuse for delaying policy action and recognising the

important health threat viral hepatitis represents to Europe. Even more so, since there is evidence that the burden will increase in years to come.' There have been important strides made to this end in Europe. However, much still needs to be done and we will only reach our goals if more funds and resources are specifically allocated, both at EU and national level, to make the fight against viral hepatitis a priority as it deserves to be.

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ANNEX I: CONFERENCE ADDRESS BY DR MARC SPRENGER, DIRECTOR OF THE EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL (ECDC)

Summary of Address: Dr Marc Sprenger, Director, European Centre for Disease Prevention and Control: The ECDC View

I. Hepatitis B and C are serious public health problems

Hepatitis B and C are serious public health problems. Every year, upwards of 7000 newly diagnosed cases of hepatitis B and more than 27 000 newly diagnosed cases of hepatitis C are reported in the EU. Many of these people go on to develop liver cancer or liver cirrhosis, as a result of these infections. Indeed, the World Health Organisation (WHO) estimates that almost 80% of primary liver cancer cases are linked to this viral hepatitis.

II. We have enough evidence to know that we must act

Here, then, you have viruses that are a leading cause of one of the most common types of cancer in Europe. This defies the distinction that health policymakers like to make between infectious and noncommunicable diseases. They often argue that noncommunicable diseases are much more important than communicable diseases, but we should be careful if we consider hepatitis B and C as infectious diseases. In a way they are, but the consequences are in a chronic disease. It also makes estimating the number of deaths attributable to hepatitis very complex. Nonetheless, I stress that we have enough evidence already to know that we need to do something. More research is always necessary, but we have a lot of knowledge now and can begin to take action.

III. Tailored national screening and vaccination programmes

In May 2010, the World Health Assembly recognized viral hepatitis, and in particular hepatitis B and C, as a global public health problem. This Summit Conference is a recognition, by the EU public health community, of the need for European-level action against viral hepatitis.

What needs to be done in Europe? This is where finding conclusions becomes a bit more difficult because the ECDC's technical reports show that the epidemiology of hepatitis B and C in Europe is very diverse. For example, some countries have significant levels of infection among the general population; in others, however, hepatitis B and C are rare among the general population. Their epidemics are concentrated in groups at risk, such as migrants from high-epidemic countries and injecting drug-users.

From data we already have, it is evident that this is not an epidemic for which the EU can devise a one-size-fits-all solution. We need solutions that are tailored to the reality of the local and national situation in European countries. More data are needed to allow us to do this tailoring, but be careful, because we have a lot of information. More prevalence surveys are needed, especially in sub-populations, and improved reporting of case-based surveillance, so that a fuller picture of the epidemics becomes available. In high-prevalence countries, universal screening and vaccination programmes might be cost-effective, if the price of test kits and vaccines is low. This is much less likely to be the case in lower-prevalence countries such as Germany, the Netherlands or the UK. In these countries, though, screening of certain high-prevalence populations such as migrants or IDUs could be cost-effective.

I am a doctor but as a public health official, I am obliged to call for evidence-informed decisions on screening and vaccination programmes which look at costs as well as, of course, the benefits. The Europe-wide evidence indicates that screening and vaccination programmes in Europe need to be tailored to suit different national epidemics. The challenge for the ECDC and the EU is to manage this huge diversity in Europe.

IV. Managing diversity – not tolerating unjustified inequalities

Managing diversity should not mean tolerating unjustified inequalities. I call on you to read the report, in which you will find a lot of evidence. Use that evidence in your countries, and have your policymakers use it. We are not able to sign the Call to Action because of reasons which I think you understand, but please use the data.

In terms of unjustified inequalities, some national differences came to light during the compilation of the ECDC's technical reports which are very difficult to justify or to accept. The most striking example is the fact that a few countries appear not to offer hepatitis B testing to pregnant women. This means that the opportunity to prevent mother-to-child transmission is lost.

I hope that, in the EU, we can at least aspire to prevention for all. Antenatal testing for hepatitis B is a very cost-effective prevention measure that should be implemented across the whole of Europe. I hope that EU solidarity means that better-resourced countries will help their poorer or less well-organized counterparts to achieve this. Rather than just talking, please act.

The EU, and particularly ECDC, has an important role to play in identifying and sharing good practice in the prevention and control of hepatitis B and C. Health interest groups and professional associations, such as the organizers of this Conference, can also make a major contribution to sharing and disseminating knowledge. By sharing this knowledge and working together to identify good practice, we can facilitate a levelling upward of hepatitis B and C prevention and control in Europe.

V. Conclusions

My conclusions are:

Hepatitis B and C are extremely serious public health problems.

We have enough evidence already to know that we need to act.

Screening and vaccination programmes are part of the answer, but must be tailored to suit different national epidemics.

Europe's health experts must work together and pool their knowledge on hepatitis B and C.

ANNEX II: CALL TO ACTION OF THE HEPATITIS B AND C SUMMIT CONFERENCE

October 15th, 2010

This Call to Action is endorsed by:
Alojz Peterle MEP
Viral Hepatitis Prevention Board
European Monitoring Centre for Drugs and Drug Addiction
European Association for the Study of the Liver
European Liver Patients Association
World Hepatitis Alliance
International Centre for Health, Migration and Development.

The Hepatitis B and Hepatitis C Summit Conference brings together a wide range of stakeholders united in their goal to encourage European and national leaders to devise effective policies and implement-targeted actions to curb the occurrence of hepatitis B and C in Europe. The Conference commends previous work in the domain of hepatitis B and C and aims to build on these initiatives, in particular the 63rd World Health Assembly's resolution on Viral Hepatitis of May 2010, MEP Thomas Ulmer's Call to Action on Hepatitis B launched at the European Parliament in 2006 and the European Parliament's Written Declaration on Hepatitis C in 2007.[1]

The Steering Group of the Hepatitis B and Hepatitis C Summit Conference, together with its partner associations, calls on the EU Member States and the European Commission to:

1 Improve awareness of the threat posed by Hepatitis B and Hepatitis C
2 Integrate prevention programmes for Hepatitis B and Hepatitis C into existing public health frameworks
3 Enhance surveillance for Hepatitis B and Hepatitis C across Europe
4 Support the development and integration of cost-effective technologies and procedures for use in viral hepatitis prevention, control and management, including screening of high risk individuals according to scientific and epidemiological based evidence
5 Ensure universal access to early counselling and treatment for persons infected with hepatitis B or hepatitis C
6 Expand research resources for hepatitis B and hepatitis C.

Improve awareness of the threat posed by hepatitis B and hepatitis C

1 The message that hepatitis B and C pose a significant threat to public health and are the leading cause of liver cancer must be continually reinforced to policymakers and to the general public.
2 Innovative and sensitive public health campaigns are needed to ensure that individuals are made aware of the risks of hepatitis B and C infection and transmission. At the same time, care should be taken to de-stigmatize viral hepatitis and encourage the social integration of people infected with hepatitis B and C.

Integrate prevention programmes for hepatitis B and hepatitis C into existing public health frameworks

1 Vaccination programmes against hepatitis B should be integrated into routine health programmes in order to reach as many individuals as possible.
2 At the same time, existing vaccination policies against hepatitis B should be reassessed to ensure that they

[1]*Of particular note are:*
- The 63rd World Health Assembly Resolution on Viral Hepatitis, adopted on 21 May 2010;
- MEP Thomas Ulmer's Call to Action on Hepatitis B launched at the European Parliament in 2006, and the European Parliament's Written Declaration on Hepatitis C requesting ia. a Council Recommendation to promote screening for Hepatitis;
- The European Parliament Report of April 2010 on the European Commission's Communication on Action Against Cancer, which 'Urges that... the prevention and control of diseases which can develop into cancer, for instance primary and secondary prevention of viral hepatitis and treatment where appropriate, should be addressed by the Cancer Partnership and in future EU initiatives, such as a revised Council recommendation on cancer screening';
- The inclusion of Hepatitis B and C in the surveillance and monitoring programmes of the European Centre for Disease Prevention and Control (ECDC) and the EMCDDA;
- Work currently undertaken by the European Association for Disease of the Liver (EASL), the European Liver Patient Association (ELPA), and the VHPB.

reflect current epidemiology and reach at-risk target groups.

3 Beside universal hepatitis B vaccination programmes aimed at reaching newborn, infants, and/or children, critical target groups include: household contacts of people infected with HBV, migrants, IDUs, prisoners, health care workers, blood donors, pregnant women and newborns and people infected with HIV.

4 Hepatitis C testing and treatment of IDUs, among whom most current hepatitis C transmission is occurring, should be considered a public health imperative and fully integrated into national substance misuse programmes.

Enhance surveillance for hepatitis B and hepatitis C across Europe

1 Comprehensive and enhanced surveillance of hepatitis B and C should be developed and implemented at the EU-level under the coordination of the European Centre for Disease Prevention and Control.

2 National protocols for disease surveillance must be harmonized with the EU framework for hepatitis B and C surveillance, which may include chronic cases of hepatitis B and C in order to convey the full burden that they pose.

Support the development and integration of cost-effective technologies and procedures for use in viral hepatitis prevention, control and management, including screening of high risk individuals according to scientific and epidemiological based evidence

1 Strengthen health systems in order to adequately provide local populations with the most cost-effective and affordable interventions in accordance with the local epidemiological situations.

2 Screening of high risk individuals should be prioritized. Legal and ethical implications should be always considered.

Ensure universal access to early counselling and treatment for persons infected with hepatitis B or hepatitis C

1 Currently available treatments are potentially curative, reducing mortality from cirrhosis and liver cancer.

2 Universal and equal access to hepatitis B and hepatitis C counselling and possible therapy must be considered a priority across Europe for their public health impact to be reduced.

3 Leadership from national governments is necessary to dispel the myth that hepatitis B and C are untreatable, and to actively promote the availability and early use of effective treatments for affected individuals in accordance with European guidelines and treatment protocols.

Expand research resources for hepatitis B and hepatitis C

1 National and EU-level research funding organizations are urged to allocate explicit funds towards research on the epidemiology, prevention and treatment of hepatitis B and C.

2 Liver disease, including hepatitis B and C, should become a priority area for future research within the seventh and eighth Research Framework Programmes of the EU.